# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 15 AUG 2008 |
| Applicant's or agent's file reference<br>77840-A-PCT/JPW/BB | FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 08/05564 | 30 April 2008 (30.04.2008) | 19 July 2007 (19.07.2007) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G01N 33/53 (2008.04)
USPC - 435/7.1

Applicant PROGENICS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No 571-273-3201 | 5 August 2008 (05.08.2008) | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (April 2007)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 23, 29-39, 121-122 and 126

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 23, 29-39, 121,122, 126 are so unclear that no meaningful opinion could be formed *(specify)*:
Claims 23, 29-39, 121, 122 and 126 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 23, 29-39, 121, 122 and 126

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-22, 24-28, 46-48, 61-95, 105, and 107-120 | YES |
| | Claims | 40-45, 49-60, 96-104, 106, and 123-125 | NO |
| Inventive step (IS) | Claims | none | YES |
| | Claims | 1-22, 24-28, 40-120, and 123-125 | NO |
| Industrial applicability (IA) | Claims | 1-22, 24-28, 40-120, and 123-125 | YES |
| | Claims | none | NO |

2. Citations and explanations:

Claims 40-45, 49-60, 96-104, 106, and 123-125 lack novelty under PCT Article 33(2) as being anticipated by US 2007/0026441 A1 to OLSON et al. (hereinafter "Olson '441").

Regarding claim 40, Olson '441 teaches a method of reducing viral load in an HIV-1-infected human subject which comprises:
-- administering to the subject an effective HIV-1 viral load reducing dose of (a) a humanized antibody designated PRO 140, or (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-1 fusion with CD4+CCR5+,
-- wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPR0140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPR0140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPR0140 (mut B+D+I)VH (ATCC Deposit Designation PTA-4099),
-- wherein the effective HIV-1 viral load-reducing dose is selected from 5 mg per kg of the subject's body weight or 10 mg/kg of the subject's body weight, so as to thereby reduce the subject's HIV-1 viral load (para [0031]).

Regarding claim 42, Olson '441 teaches a method of reducing viral load in an HIV-1-infected human subject which comprises:
-- subcutaneously administering (para [0074]) to the subject an effective HIV-1 viral load reducing dose of (a) a humanized antibody designated PRO 140, or (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-1 fusion with CD4+CCR5+ cells,
-- wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPR0140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPR0140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPR0140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099),
-- wherein the effective subcutaneous HIV-1 viral load-reducing dose is 2-10 mg/kg of the subject's body weight, so as to thereby reduce the subject's HIV-1 viral load (para [0031]).

Regarding claim 96, Olson '441 teaches a CCR5 receptor antagonist (para [0028]) which, when administered to an HIV-infected subject, achieves an HIV RNA reduction of 1.20 log10 to 1.83 log10 (fig 5) by about day nine or day ten following administration to the subject (para [0046]-[0047]).

Regarding claim 97, Olson '441 teaches a CCR5 receptor antagonist (para [0028]) which, when administered to an HIV-infected subject, achieves a log10 HIV RNA change of from about -1.0 to about -1.7 (fig 5) in the subject by about day five to day ten following administration to the subject (para [0046]-[0047]).

Regarding claim 98, Olson '441 teaches a CCR5 receptor antagonist (para [0028]) which, when administered to an HIV-infected subject, results in a greater than ten-fold decrease (fig 5) in HIV RNA in the subject at about ten days following administration to the subject (para [0046]-[0047]).

Regarding claim 99, Olson '441 teaches a CCR5 receptor antagonist (para [0028]) which, when administered to an HIV-infected subject, results in a greater than or equal to 1 log10 decrease (fig 5) in HIV RNA in the subject at about day five to about day fifteen following administration to the subject (para [0046]-[0047]).

Regarding claims 41, 43 and 103, Olson '441 further teaches the HIV-1 viral load reducing dose is 5 mg/kg of the subject's body weight or 10 mg per kg of the subject's body weight (para [0031]).

Regarding claim 44, Olson '441 also teaches the effective HIV-I viral load-reducing dose is a total of 150 mg or 300 mg (para [0269]).

Regarding claim 45, Olson '441 further teaches the effective HIV-I viral load reducing dose is administered subcutaneously (para [0074]) QI week or Q2 weeks, or one or more times per week or one or more times every two weeks (para [0131]).

Regarding claims 49 and 102, Olson '441 also teaches PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPR0140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded by the plasmid designated pVg4:HuPR0140 HG2-VH (ATCC Deposit Designation PTA-4098) (para [0104]).——continued in supplemental Box 1 ——

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2). Citations and explanations:

Regarding claim 50, Olson '441 further teaches the administration of the humanized antibody designated PRO 140 of (a), or the anti-CCR5 receptor monoclonal antibody of (b) is via an intravenous route (para [0074]).

Regarding claim 51, Olson '441 also teaches the viral load-reducing dose is sufficient to achieve in the subject a serum concentration of the antibody of at least 400ng/ml (para [0097]).

Regarding claim 52, Olson '441 further teaches the viral load-reducing dose is sufficient to achieve and maintain in the subject a serum concentration of the antibody selected from the group consisting of at least 1 ug/ml, about 3 to about 12 ug/ml, at least 5ug/ml, at least 10 ug/ml, at least 25 ug/ml and at least 50 ug/ml (para [0097]).

Regarding claim 53, Olson '441 also teaches the reduction of the subject's HIV-I viral load is maintained for at least one week (para [0098]).

Regarding claim 54, Olson '441 further teaches the reduction of the subject's HIV-I viral load is maintained for at least two weeks, for at least four weeks, or for at least three months (para [0098]).

Regarding claim 55, Olson '441 also teaches the subject's HIV-I viral load is reduced by at least 50% following administration of the CCR5 receptor antagonist or the antibody (para [0099]).

Regarding claim 56, Olson '441 further teaches the subject's HIV-I viral load is reduced by at least 70% following administration of the antibody, by at least 90% following administration of the antibody (para [0099]).

Regarding claim 57, Olson '441 also teaches co-administering to the subject at least one additional antiretroviral agent effective against HIV (para [0100]).

Regarding claim 58, Olson '441 further teaches the antiretroviral agent is a nonnucleoside reverse transcriptase inhibitor (NNRTI), a nucleoside reverse transcriptase inhibitor (NRTI), a protease inhibitor (PI), a fusion inhibitor, or any combination thereof (para [0101]).

Regarding claim 59, Olson '441 also teaches the antiretroviral agent is at least one additional CCR5 receptor antagonist that does not compete with the humanized monoclonal antibody designated PRO 140 (para [0293]).

Regarding claim 60, Olson '441 further teaches the subject is treatment na.ve or treatment-experienced (para [0100]).

Regarding claim 100, Olson '441 also teaches the CCR5 receptor antagonist (para [0095]) is selected from (a) a humanized antibody designated PRO 140, or (b) an anti-CCR5 receptor monoclonal antibody which (i) binds to CD4+CCR5+ cells in the subject and inhibits fusion of HIV-I with such cells, (ii) inhibits HIV-I fusion with CD4+CCR5+ cells with a potency equal or greater than that of PRO 140, (iii) coats CD4+CCR5+ cells in the subject without reducing the number of such cells in the subject, and/or (iv) binds to the subject's CD4+CCR5+ cells without inducing an increase in the subject's plasma concentration of circulating I3-chemokines, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140VK(ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA4099) (para [0094]).

Regarding claim 101, Olson '441 further teaches viral load reduction in the subject persists for about two to three weeks (para [0098]).

Regarding claim 104, Olson '441 also teaches the CCR5 receptor antagonist is administered intravenously or subcutaneously (para [0074]).

Regarding claim 106, Olson '441 further teaches a pharmaceutically acceptable carrier (para [0140]).
Regarding claim 123, Olson '441 also teaches co-administering an HIV entry inhibitor which is an antibody (para [0217], 2D7).
Regarding claim 124, Olson '441 further teaches the HIV entry inhibitor antibody is a monoclonal antibody (para [0217]).
Regarding claim 125, Olson '441 also teaches a humanized antibody that is TNX-355 (para [0009]).

Claims 46 and 95 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441, as above.

Regarding claim 46, Olson '441 teaches the effective viral load reducing dose administered subcutaneously reduces HIV-1 viral load by 1.5-1.8 log10 (para [0046]-[0047], fig 5). Olson '441 does not teach 1.5-2 log10. Since the range of Olson '441 significantly overlaps the range of claim 46, one of ordinary skill in this art would recognize that it is obvious over it.

Regarding claim 95, Olson '441 teaches a CCR5 receptor antagonist which, when administered to an HIV-infected subject, achieves an average maximum decrease of viral load in the subject of up to 1.8 log10 by about day nine to day fifteen following administration to the subject (para [0046]-[0047], fig 5).
Olson '441 does not teach up to 2.5 log10. It would have been obvious to one of ordinary skill in this art based on routine experimentation to select a dosage and administration pattern that achieves an average maximum decrease of viral load in the subject of up to 2.5 log10 by about day nine to day fifteen following administration to the subject.

----------Please see Supplemental Box 2 to continue ----------

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**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V(2) and the preceding Supplemental Box 1:

Claims 1-22, 24-26, 47, 48, 81-93 and 107-118 lack an inventive step under PCT Article 33(3) as being obvious over an abstract entitled "Efficacy and Safety of Maraviroc plus Optimized Background Therapy in Viremic, ART-experienced Patients Infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-Week Results" by NELSON et al (hereinafter 'Nelson') in view of Olson '441.

Regarding claim 1, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the viral load reducing dose of the CCR5 receptor antagonist achieves an HIV RNA reduction of up to about 2.0 log10 in the subject following administration of the CCR5 receptor antagonist (pg 1, table, ln 1).
While Nelson discloses that the reduction was over a 24 week period (pg 1, para 3, ln 5), Nelson does not teach an HIV RNA reduction of up to about 2.5 log10. Olson '441 teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (para [0031]). Olson also teaches a viral load reducing dose of the CCR5 receptor antagonist achieves an HIV RNA reduction of up to about 1.8 log10 in a subject following administration of the CCR5 receptor antagonist where the subject is a mouse (para [0046]-[0047], fig 5) over a 12 day period (Fig 5). It would have been obvious to one of ordinary skill in this art based on routine experimentation to combine the methods of Nelson and Olson '441 to achieve an HIV RNA reduction of up to about 2.5 log10. One of ordinary skill in this art would have been motivated to do so because Olson '441's method shows an equivalent HIV RNA reduction over 1/14 the time period.

Regarding claim 3, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-1 viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the viral load reducing dose of the CCR5 receptor antagonist achieves a mean log10 HIV RNA change of from about -1.97 (pg 1, table, ln 1) in the subject by about day 168 (pg 1, para 3, ln 5) following administration of the CCR5 receptor antagonist.
Olson '441 teaches a method of reducing viral load in an HIV-I-infected subject which comprises administering to the subject an effective HIV-1 viral load reducing dose of a CCR5 receptor antagonist (para [0028], [0031]), as well as a viral load reducing dose of the CCR5 receptor antagonist achieves a mean log10 HIV RNA change of from about -1.0 to about -1.7 in the subject by about day five to about day ten following administration of the CCR5 receptor antagonist wherein the subject is a mouse (para [0046]-[0047], fig 5). It would have been obvious to one of ordinary skill in this art to use the method of Olson '441 on humans as in Nelson. One of ordinary skill in this art would have been motivated to do so because Olson '441's method shows an equivalent HIV RNA reduction over about 1/14 the time period.

Regarding claim 4, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the effective HIV-1 viral load reducing dose results in a greater than tenfold decrease in HIV RNA (pg 1, table, ln 1) in the subject at about 168 days following administration of the CCR5 receptor antagonist (pg 1, para 3, ln 5).
Nelson does not teach the reduction occurs at about ten days following administration. Olson '441 teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (para [0031]). Olson also teaches an effective HIV-1 viral load reducing dose that results in a greater than tenfold decrease in HIV RNA in the subject at about ten days following administration of the CCR5 receptor antagonist (para [0046]-[0047], Fig 5) wherein the subject is a mouse. It would have been obvious to one of ordinary skill in this art to use the method of Olson '441 on humans as in Nelson. One of ordinary skill in this art would have been motivated to do so because Olson '441's method shows an equivalent HIV RNA reduction over about 1/14 the time period.

Regarding claim 5, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the effective HIV-1 viral load reducing dose results in a > or = to 1 log10 reduction in HIV RNA (pg 1, table, ln 1) in the subject at about 168 days following administration of the CCR5 receptor antagonist (pg 1, para 3, ln 5).
Nelson does not teach the reduction occurs at about day 5 to about day 15 following administration of the CCR5 receptor antagonist.
Olson '441 teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (para [0031]), as well as an effective HIV-1 viral load reducing dose results in a > or = to 1 log10 reduction in HIV RNA in a subject at about day 5 to about day 15 following administration of the CCR5 receptor antagonist (para [0046]-[0047], Fig 5) wherein the subject is a mouse. It would have been obvious to one of ordinary skill in this art to use the method of Olson '441 on humans as in Nelson. One of ordinary skill in this art would have been motivated to do so because Olson '441's method shows an equivalent HIV RNA reduction over about 1/14 the time period.

Regarding claim 47, Nelson teaches a method of elevating CD4+ cell count (pg 2, para 1) in an HIV-1-infected human subject which comprises:
-- administering to the subject an effective CD4+ cell count-elevating dose of a CCR5 receptor antagonist (pg 1, para 1).
Nelson does not teach an anti-CCR5 receptor monoclonal antibody. Olson '441 teaches a CCR5 receptor antagonist (para [0028]) that is (a) a humanized antibody designated PRO 140, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099) (para [0031]).
Olson '441 also teaches an effective HIV-1 viral load-reducing dose of it comprises from 0.1 mg per kg to 10 mg per kg of the subject's body weight. Olson further teaches "In many instances, mAbs provide safety, efficacy and ease-of-use profiles that are unrivalled by small-molecule compounds." (para [0027]). It would have been obvious to one of ordinary skill in this art to use the anti-CCR5 receptor monoclonal antibody of Olson '441 in the method of Nelson. One of ordinary skill in this art would have been motivated to do so for the benefits mAbs provide taught by Olson '441. It would have been obvious to one of ordinary skill in this art based on routine experimentation to have the effective CD4+ cell count-elevating dose be selected from 0.1 mg per kg to 25 mg per kg of the subject's body weight.

---------- Please see the following Supplemental Box 3 ----------

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**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2) and the preceding Supplemental Box 2:

Regarding claim 81, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the viral load reducing dose of the CCR5 receptor antagonist achieves an up to 2.0 log10 HIV RNA reduction (pg 1, table, ln 1) by about day 168 following administration, so as to reduce the subject's HIV-I viral load (pg 1, para 3, ln 5).
Nelson does not teach an anti-CCR5 receptor monoclonal antibody nor an up to 2.5 log10 HIV RNA reduction by about day nine or day ten. Olson '441 teaches method of reducing viral load in an HIV-I-infected human subject which comprises:
-- administering to the subject an effective HIV-I viral load reducing dose of (a) a humanized antibody designated PRO 140, or of (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells,
-- wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain compnsing the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+Q-VH (ATCC Deposit Designation PTA-4099) (para [0031]).
Olson '441 also teaches an effective HIV-I viral load-reducing dose achieves an up to 1.8 log10 HIV RNA reduction by about day nine or day ten following administration, so as to reduce the subject's HIV-I viral load wherein the subject is a mouse (para [0046]-[0047], fig 5). Olson further teaches "In many instances, mAbs provide safety, efficacy and ease-of-use profiles that are unrivalled by small-molecule compounds." (para [0027]). It would have been obvious to one of ordinary skill in this art to use the anti-CCR5 receptor monoclonal antibody of Olson '441 in the method of Nelson. One of ordinary skill in this art would have been motivated to do so for the benefits mAbs provide taught by Olson '441. It would have also been obvious to one of ordinary skill in this art based on routine experimentation to achieve an HIV RNA reduction of up to about 2.5 log10 by about day nine or day ten following administration.

Regarding claim 82, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises
-- administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the viral load reducing dose of the CCR5 receptor antagonist achieves an up to 2.0 log10 HIV RNA reduction (pg 1, table, ln 1) by about day 168 following administration, so as to reduce the subject's HIV-I viral load (pg 1, para 3, ln 5).
Nelson does not teach an anti-CCR5 receptor monoclonal antibody nor an up to 2.5 log10 HIV RNA reduction by about day nine or day ten. Olson '441 teaches method of reducing viral load in an HIV-I-infected human subject which comprises:
-- administering to the subject an effective HIV-I viral load reducing dose of (a) a humanized antibody designated PRO 140, or of (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells,
-- wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+Q-VH (ATCC Deposit Designation PTA-4099) (para [0031]).
Olson '441 also teaches an effective HIV-I viral load-reducing dose that achieves a 1.20 log10 to 1.83 log10 HIV RNA reduction by about nine to ten days following administration, so as to reduce the subject's HIV-I viral load wherein the subject is a mouse (para [0046]-[0047], fig 5). Olson further teaches "In many instances, mAbs provide safety, efficacy and ease-of-use profiles that are unrivalled by small-molecule compounds." (para [0027]). It would have been obvious to one of ordinary skill in this art to use the anti-CCR5 receptor monoclonal antibody of Olson '441 in the method of Nelson. One of ordinary skill in this art would have been motivated to do so for the benefits mAbs provide taught by Olson '441. It would have also been obvious to one of ordinary skill in this art based on routine experimentation to achieve an effective HIV-I viral load-reducing dose achieves a 1.20 log10 to 1.83 log10 HIV RNA reduction by about nine to ten days following administration, so as to reduce the subject's HIV-I viral load.

Regarding claim 83, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises
-- administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the viral load reducing dose of the CCR5 receptor antagonist achieves an up to 2.0 log10 HIV RNA reduction (pg 1, table, ln 1) by about day 168 following administration, so as to reduce the subject's HIV-I viral load (pg 1, para 3, ln 5).
Nelson does not teach an anti-CCR5 receptor monoclonal antibody nor an up to 2.5 log10 HIV RNA reduction by about day nine or day ten. Olson '441 toaches method of reducing viral load in an HIV-I-infected human subject which comprises:
-- administering to the subject an effective HIV-I viral load reducing dose of (a) a humanized antibody designated PRO 140, or of (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+Q-VH (ATCC Deposit Designation PTA-4099) (para [0031]).
Olson '441 also teaches an effective HIV-1 viral load-reducing dose results in a suppression of viral load by at least 1.0 log10 within about five days following administration, so as to reduce the subject's HIV-1 viral load wherein the subject is a mouse (para [0046]-[0047], fig 5). Olson further teaches "In many instances, mAbs provide safety, efficacy and ease-of-use profiles that are unrivalled by small-molecule compounds." (para [0027]). It would have been obvious to one of ordinary skill in this art to use the anti-CCR5 receptor monoclonal antibody of Olson '441 in the method of Nelson. One of ordinary skill in this art would have been motivated to do so for the benefits mAbs provide taught by Olson '441. It would have also been obvious to one of ordinary skill in this art based on routine experimentation to achieve an effective HIV-1 viral load-reducing dose results in a suppression of viral load by at least 1.0 log10 within about five days following administration, so as to reduce the subject's HIV-1 viral load.

----------Please see the following Supplemental Box 4 ----------

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V(2) and the preceding Supplemental Box 3:

Regarding claim 84, Nelson teaches a method of reducing viral load in an HIV-I-infected human subject which comprises
-- administering to the subject an effective HIV-I viral load reducing dose of a CCR5 receptor antagonist (pg 1 para 1),
-- wherein the viral load reducing dose of the CCR5 receptor antagonist achieves an up to 2.0 log10 HIV RNA reduction (pg 1, table, ln 1) by about day 168 following administration, so as to reduce the subject's HIV-I viral load (pg 1, para 3, ln 5).
Nelson does not teach an anti-CCR5 receptor monoclonal antibody nor an up to 2.5 log10 HIV RNA reduction by about day nine or day ten. Olson '441 teaches method of reducing viral load in an HIV-I-infected human subject which comprises:
-- administering to the subject an effective HIV-I viral load reducing dose of (a) a humanized antibody designated PRO 140, or of (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+Q-VH (ATCC Deposit Designation PTA-4099) (para [0031]).
Olson '441 also teaches an effective HIV-I viral load-reducing dose results in a greater than ten fold decrease in HIV RNA in the subject by about ten days following administration, so as to reduce the subject's HIV-1 viral load wherein the subject is a mouse (para [0046]-[0047], fig 5).
Olson further teaches that "[i]n many instances, mAbs provide safety, efficacy and ease-of-use profiles that are unrivalled by small-molecule compounds." (para [0027]). It would have been obvious to one of ordinary skill in this art to use the anti-CCR5 receptor monoclonal antibody of Olson '441 in the method of Nelson. One of ordinary skill in this art would have been motivated to do so for the benefits mAbs provide taught by Olson '441. It would have also been obvious to one of ordinary skill in this art based on routine experimentation to achieve an effective HIV-I viral load-reducing dose results in a greater than ten fold decrease in HIV RNA in the subject by about ten days following administration, so as to reduce the subject's HIV-1 viral load.

Regarding claims 107, Nelson teaches a method of reducing vira load in an HIV-1-infected subject, which comprises:
(a) determining that the subject is infected with a CCR5-tropic strain ofHIV-1; and
(b) administering to the subject an effective HIV-1 vira110ad reducing dose of a CCR5 receptor antagonist (pg 1 para 1).
Nelson does not teach CCR5 receptor antagonist which is selected from (a) a humanized antibody designated PRO 140, or (b) an anti-CCR5 receptor monoclonal antibody. Olson '441 teaches method of reducing viral load in an HIV-I-infected human subject which comprises:
-- subcutaneously administering to the subject an effective HIV-I viral load reducing dose of (a) a humanized antibody designated PRO 140, or of (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells,
-- wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+Q-VH (ATCC Deposit Designation PTA-4099) (para [0031]).
Olson further teaches that "[i]n many instances, mAbs provide safety, efficacy and ease-of-use profiles that are unrivalled by small-molecule compounds." (para [0027]). It would have been obvious to one of ordinary skill in this art to use the anti-CCR5 receptor monoclonal antibody of Olson '441 in the method of Nelson. One of ordinary skill in this art would have been motivated to do so for the benefits mAbs provide taught by Olson '441.

Regarding claim 2, Olson '441 teaches viral load reducing dose of the CCR5 receptor antagonist achieves an HIV RNA reduction of from 1.20 log10 to 1.83 log10 in the subject following administration of the CCR5 receptor antagonist wherein the subject is a mouse (para [0046]-[0047], fig 5). It would have also been obvious to one of ordinary skill in this art based on routine experimentation to have a viral load reducing dose of the CCR5 receptor antagonist that achieves an HIV RNA reduction of from 1.20 log10 to 1.83 log10 in the subject following administration of the CCR5 receptor antagonist in a human.

Regarding claim 6, it would have also been obvious to one of ordinary skill in this art based on routine experimentation to have the > or = to 1 log10 reduction in HIV RNA persist in a human subject for about ten days to about three weeks.

Regarding claim 7, Olson '441 further teaches the HIV RNA reduction occurs by about day 9 to about day 15 after administering to the subject the effective HIV-1 viral load reducing dose (fig 5).

Regarding claim 8, Olson '441 additionally teaches the HIV RNA reduction occurs by about day 10 after administering to the subject the effective HIV-I viral load reducing dose (fig 5).

Regarding claim 9, Olson '441 also teaches the viral load reducing dose of the CCR5 receptor antagonist is a single dose administered intravenously (para [0074]).

Regarding claim 10, Olson '441 further teaches the viral load reducing dose of the CCR5 receptor antagonist is a multiple dose administered intravenously (para [0074]).

Regarding claims 11, 12, 87, and 115, Olson '441 also teaches the HIV-1 viral load reducing dose is 5 mg/kg of the subject's body weight or 10 mg per kg of the subject's body weight (para [0031]).

Regarding claim 13, Olson '441 further teaches the viral load reducing doses of the CCR5 receptor antagonist are administered about every two weeks, about every four weeks, or about every six weeks after administration of a first dose (para [0098]).

---------- Please see the following Supplemental Box 5 ----------

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V(2) and the preceding Supplemental Box 4:

Regarding claim 14, Olson '441 also teaches the viral load reducing doses of the CCR5 receptor antagonist are administered at repeated intervals (para [0074]) of about every two weeks, about every three weeks, or about every six weeks after administration of a first dose (para [0098]).

Regarding claim 15, Olson '441 further teaches the viral load reducing dose of the CCR5 receptor antagonist is administered subcutaneously (para [0074]).

Regarding claim 16, Olson '441 also teaches the viral load reducing dose of the CCR5 receptor antagonist is a multiple dose administered subcutaneously (para [0074]).

Regarding claim 17, Nelson further teaches the viral load reducing dose of the CCR5 receptor antagonist reduces viral load by 1.5-2 log10 (pg 1, table, ln 1).

Regarding claim 18, Olson '441 also teaches the viral load reducing dose of the CCR5 receptor antagonist is 2-10 mg/kg (para [0031]) of the subject's body weight administered subcutaneously (para [0074]).

Regarding claim 19, Olson '441 further teaches the viral load reducing dose of the CCR5 receptor antagonist is administered subcutaneously (para [0074]) Q2weeks (para [0098]).

Regarding claim 20, Olson '441 also teaches the viral load reducing dose of the CCR5 receptor antagonist is administered subcutaneously one or more times (para [0074]) per week or one or more times every two weeks (para [0098]).

Regarding claims 21, 22, 25, 85, and 108, Olson '441 further teaches the CCR5 receptor antagonist is selected from (a) a humanized antibody designated PRO 140, or (b) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-1 fusion with CD4+CCR5+ cells, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPR0140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPR0140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+Q-VH (ATCC Deposit Designation PTA-4099) (para [0031]).

Regarding claim 24, Olson '441 also teaches the anti-CCR5 receptor monoclonal antibody is a humanized, human, or chimeric antibody (para [0075]).

Regarding claim 26, Olson '441 further teaches the PRO 140 is administered intravenously in a single 5 mg/ml dose [0167] and a 1.8 log10 mean reduction in HIV RNA (fig 5). It would have been obvious to one of ordinary skill in this art based on routine experimentation to have the PRO 140 administered intravenously in a single 5 mg/ml dose result in a 1.8 log10 mean reduction in HIV RNA.

Regarding claim 48, Olson '441 also teaches a dose that is selected from 5 mg/kg, or 10 mg/kg, of the subject's body weight (para [0031]).
Regarding claim 86, Olson '441 further teaches the reduction of viral load in the subject persists for about two to three weeks (para [0098]).

Regarding claim 88 and 114, Olson '441 also teaches the viral load reducing dose is administered intravenously, or subcutaneously (para [0074]).

Regarding claim 89, Olson '441 further teaches the subject is treatment-naive or treatment experienced (para [0100]).

Regarding claim 90, Olson '441 also teaches (a) prior to administering the humanized antibody designated PRO 140, or the anti-CCR5 receptor monoclonal antibody to the subject, the subject has received treatment with at least one antiretroviral agent effective to inhibit HIV1, and/or (b) concurrent with administering the humanized antibody designated PRO 140, or the anti-CCR5 receptor monoclonal antibody at least one antiretroviral agent is administered to the subject, so as to enhance the reduction of HIV-1 viral load in the subject (para [0101]).

Regarding claim 91, Olson '441 further teaches the antiretroviral agent is a nonnucleoside reverse transcriptase inhibitor (NNRTI), a nucleoside reverse transcriptase inhibitor (NRTI), a protease inhibitor (PI), a fusion inhibitor, or any combination thereof (para [0101]).

Regarding claim 92, Olson '441 also teaches the antiretroviral agent is a CCR5 receptor antagonist (para [0105]).
Regarding claim 93, Olson '441 further teaches the CCR5 receptor antagonist is a non-protein small organic molecule (para [0105]).

Regarding claim 109, Olson '441 also teaches a CCR5 receptor antagonist which, when administered to an HIV-infected subject, achieves an average maximum decrease of viral load in the subject of up to 1.8 log10 by about day nine to day fifteen following administration to the subject (para [0046]-[0047], fig 5). Olson '441 does not teach up to 2.5 log10. It would have been obvious to one of ordinary skill in this art based on routine experimentation to select a dosage and administration pattern that achieves an average maximum decrease of viral load in the subject of up to 2.5 log10 by about day nine to day fifteen following administration to the subject.

Regarding claim 110, Olson '441 further teaches a CCR5 receptor antagonist that achieves an HIV RNA reduction of from 1.20 log10 to 1.83 log10 by about day nine or day ten following administration (para [0046]-[0047], Fig 5).

Regarding claim 111, Olson '441 also teaches a CCR5 receptor antagonist that achieves a log10 HIV RNA change of from about -1.0 to about -1.7 in the subject by about day five to day ten following administration (para [0046]-[0047], fig 5).

Please see the following Supplemental Box 6

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2) and the preceding Supplemental Box 5:

Regarding claim 112, Olson '441 further teaches a CCR5 receptor antagonist that achieves a greater than ten-fold decrease in HIV RNA in the subject at about ten days following administration (para [0046]-[0047], fig 5).

Regarding claim 113, Olson '441 also teaches a CCR5 receptor antagonist that achieves a greater than or equal to 1 log10 decrease in HIV RNA in the subject at about day five to about day fifteen following administration (para [0046]-[0047], fig 5).

Regarding claim 116, Nelson further teaches a determination that the subject is infected with a CCR5-tropic strain of HIV is made prior to the administration of the CCR5 receptor antagonist to the subject (pg 1 para 1).

Regarding claim 117, Nelson also teaches monitoring the subject at predetermined intervals during the administration of the CCR5 receptor antagonist to determine viral load, and CD4 cell count (pg 1-2, table).

Regarding claim 118, Nelson further teaches monitoring is carried out about once every two to six months, or two to six times a year (pg 1 para 1).

Claims 61-80 and 119-120 lack inventive step under PCT Article 33(3) as being obvious over US 2006/0154857 A1 to REDFIELD et al. (hereinafter 'Redfield') in view of Olson '441.

Regarding claim 61, Redfield teaches a method of maintaining a reduced viral load in an HIV-I-infected human subject (para [0028]-[0030]), which comprises:
(a) administering to the subject an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells (para [0019], [0021]).
(b) administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the antiCCR5 receptor monoclonal antibody ("Moreover, HIV therapy is now thought to be a life-long process," para [0070]).
Redfield does not teach the first effective HIV-1 viral load-reducing dose results in a viral load reduction of up to about 2.5 log10 in the subject by about day 9 to about day 15 following dosing of the subject nor administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the antiCCR5 receptor monoclonal antibody of at a time when the subject's reduction in viral load is determined to be about 0.7 to 1.5 log10, so as to thereby maintain a reduced viral load in the subject.
Olson '441 teaches a method of reducing viral load in an HIV-I-infected subject, which comprises:
-- administering to the subject a first effective HIV-1 viral load reducing dose of (1) a humanized antibody designated PRO 140, or of (2) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099) (para [0031]),
-- wherein the first effective HIV-1 viral load-reducing dose results in a viral load reduction of up to about 2.0 log10 in the subject by about day 9 to about day 15 following dosing of the subject (para [0046]-[0047], fig 5).
Olson '441 also teaches administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the humanized antibody designated PRO 140 of (a)(1) or the antiCCR5 receptor monoclonal antibody of (a)(2) (para [0074]). It would have been obvious to one of ordinary skill in this art based on the teachings of Redfield and Olson '441 and routine experimentation to have the first effective HIV-1 viral load-reducing dose result in a viral load reduction of up to about 2.5 log10 in the subject by about day 9 to about day 15 following dosing of the subject and administer to the subject one or more subsequent effective HIV-1 viral load reducing doses of the humanized antibody designated PRO 140 of (a)(1) or the antiCCR5 receptor monoclonal antibody of (a)(2) at a time when the subject's reduction in viral load is determined to be about 0.7 to 1.5 log10. One of ordinary skill in this art would have been motivated to do so to optimize the timing and conditions for reducing and maintaining a reduced viral load in an HIV-1-infected human subject.

Regarding claim 62, Redfield teaches a method of maintaining a reduced viral load in an HIV-I-infected human subject (para [0028]-[0030]), which comprises:
(a) administering to the subject an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells (para [0019], [0021]).
(b) administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the antiCCR5 receptor monoclonal antibody ("Moreover, HIV therapy is now thought to be a life-long process," para [0070]).
Redfield does not teach the load-reducing dose results in an up to 2.5 log10 reduction in HIV-1 RNA by about day 9 to about day 15 following dosing of the subject nor administering to the subject one or more subsequent effective HIV-I viral load reducing doses of the CCR5 receptor antagonist at a time when the subject's reduction in viral load is determined to be about 0.7 to 1.5 log10. Olson '441 teaches a method of reducing viral load in an HIV-1-infected subject which compnses:
-- administering to the subject a first effective HIV-1 viral load reducing dose of a CCR5 receptor antagonist (para [0028], wherein the first effective HIV-1 viral load-reducing dose results in an up to 2.0 log10 reduction in HIV-1 RNA by about day 9 to about day 15 following dosing of the subject (para [0046]-[0047], fig 5).
Olson '441 also teaches administering to the subject one or more subsequent effective HIV-I viral load reducing doses of the CCR5 receptor antagonist (para [0074]).

----------Please see the following Supplemental Box 7 ----------

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V(2) and the preceding Supplemental Box 6:
Regarding claim 62 continues:

It would have been obvious to one of ordinary skill in this art based on the teachings of Redfield and Olson '441 and routine experimentation to have the first effective HIV-1 viral load-reducing dose result in a viral load reduction of up to about 2.5 log10 in the subject by about day 9 to about day 15 following dosing of the subject and administer to the subject one or more subsequent effective HIV-1 viral load reducing doses of the CCR5 receptor antagonist at a time when the subject's reduction in viral load is determined to be about 0.7 to 1.5 log10. One of ordinary skill in this art would have been motivated to do so to optimize the timing and conditions for reducing and maintaining a reduced viral load in an HIV-1-infected human subject.

Regarding claim 119, Redfield teaches a method of maintaining a reduced viral load in an HIV-1-infected human subject (para [0028]-[0030]), which comprises:
(a) administering to the subject an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells (para [0019], [0021]).
(b) administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the antiCCR5 receptor monoclonal antibody ("Moreover, HIV therapy is now thought to be a life-long process," para [0070]).
Redfield does not teach the first effective HIV-1 viral load-reducing dose results in a viral load reduction of up to about 1.8 log10 in the subject by about day 9 or 10 following dosing of the subject nor administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the antiCCR5 receptor monoclonal antibody at a time when the subject's reduction in viral load is determined to be about 0.7 to 1.5 log10, so as to thereby maintain a reduced viral load in the subject.
Olson '441 teaches a method of reducing viral load in an HIV-I-infected subject, which comprises:
-- administering to the subject a first effective HIV-1 viral load reducing dose of (1) a humanized antibody designated PRO 140, or of (2) an anti-CCR5 receptor monoclonal antibody which inhibits HIV-I fusion with CD4+CCR5+ cells, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099) (para [0031]), wherein the first effective HIV-1 viral load-reducing dose results in a viral load reduction of up to about 1.8 log10 in the subject by about day 9 or 10 following dosing of the subject (para [0046]-[0047], fig 5).
Olson '441 also teaches administering to the subject one or more subsequent effective HIV-1 viral load reducing doses of the humanized antibody designated PRO 140 of (a)(1) or the antiCCR5 receptor monoclonal antibody of (a)(2) (para [0074]). It would have been obvious to one of ordinary skill in this art based on the teachings of Redfield and Olson '441 and routine experimentation to have the first effective HIV-1 viral load-reducing dose result in a viral load reduction of up to about 1.8 log10 in the subject by about day 9 or 10 following dosing of the subject and administer to the subject one or more subsequent effective HIV-1 viral load reducing doses of the humanized antibody designated PRO 140 of (a)(1) or the antiCCR5 receptor monoclonal antibody of (a)(2) at a time when the subject's reduction in viral load is determined to be about 0.7 to 1.5 log10. One of ordinary skill in this art would have been motivated to do so to optimize the timing and conditions for reducing and maintaining a reduced viral load in an HIV-1-infected human subject.

Regarding claim 63, Olson '441 further teaches the first effective HIV-I viral load-reducing dose results in a viral load reduction of up to about 1.8 log10 in the subject by about day 9 to about day 15 following dosing of the subject. (para [0046]-[0047], fig 5).

Regarding claim 64, Redfield and Olson '441 do not teach the one or more subsequent effective HIV-1 viral load reducing doses are administered at a time when the subject's viral load reduction is 1.0 log10. It would have been obvious to one of ordinary skill in this art based on the teachings of Redfield and Olson '441 and routine experimentation to have the one or more subsequent effective HIV-1 viral load reducing doses are administered at a time when the subject's viral load reduction is 1.0 log10.

Regarding claims 65 and 66, Olson '441 also teaches an HIV-1 viral load reducing dose is 5 mg/kg of the subject's body weight or 10 mg per kg of the subject's body weight (para [0031]).

Regarding claim 67, Olson '441 further teaches HIV-1 viral load reducing doses administered about every two weeks, about every three weeks, about every four weeks, about once a month, or about every six weeks (para [0098]).

Regarding claim 68, Olson '441 also teaches HIV-1 viral load reducing doses are administered intravenously or subcutaneously to the subject (para [0074]).

---------- Please see the following Supplemental Box 8 ----------

International application No.
PCT/US 08/05564

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V(2) and the preceding Supplemental Box 7:

Regarding claims 69 and 120, Olson '441 further teaches PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) (para [0031]).

Regarding claims 70 and 77, Olson '441 also teaches (a) prior to administering the humanized antibody designated PRO 140 of (a)(I) or the anti-CCR5 receptor monoclonal antibody of (a)(2) to the subject, the subject has received treatment with at least one antiretroviral agent effective to inhibit HIV-1, and/or (b) concurrent with administering the humanized antibody designated PRO 140 of (a)(1) or the anti-CCR5 receptor monoclonal antibody of (a)(2), at least one antiretroviral agent is administered to the subject, so as to enhance the reduction of HIV-I viral load in the subject (para [0101]).

Regarding claims 71 and 78, Olson '441 further teaches the antiretroviral agent is a nonnucleoside reverse transcriptase inhibitor (NNRTI), a nucleoside reverse transcriptase inhibitor (NRTI), a protease inhibitor (PI), a fusion inhibitor, or any combination thereof (para [0101]).

Regarding claim 72, Olson '441 also teaches the antiretroviral agent is a CCR5 receptor antagonist (para [0105]).

Regarding claim 73 and 74 and 80, Redfield also teaches antiretroviral agent that is a CCR5 receptor antagonist that is a monoclonal antibody (para [0021]).

Regarding claim 75, Olson '441 further teaches a monoclonal antibody CCR5 receptor antagonist that IS a humanized antibody (para [0075]).

Regarding claim 76, Olson '441 also teaches humanized antibody CCR5 receptor antagonist other than the humanized antibody designated PRO 140 (para [0031]).

Regarding claim 79, Olson '441 further teaches the CCR5 receptor antagonist is a non-protein small organic molecule (para [0105]).

Claims 105 lacks inventive step under PCT Article 33(3) as being obvious over Olson '441, as above, in view of US 2007/0031408 A1 to OLSON et al (hereinafter 'Olson '408').

Regarding claim 105, Olson '441 does not teach the humanized PRO 140 antibody is pegylated to increase its serum half-life. Olson '408 teaches the humanized PRO 140 antibody (para [0007]) is pegylated to increase its serum half-life (para [0173]-[0175]). It would have been obvious to one of ordinary skill in this art to use the PRO 140 antibody of Olson '408 for the CCR5 receptor antagonist of Olson '441. One of ordinary skill in this art would have been motivated to do so to increase the length of time between dose administrations for cost reduction.

Claims 27 and 28 lack inventive step under PCT Article 33(3) as being obvious over Nelson in view of Olson '441, as above, and further in view of Olson '408.

Regarding claims 27-28, Olson '441 does not teach the humanized PRO 140 antibody is modified to increase its serum half-life by pegylation. Olson '408 teaches a humanized PRO 140 antibody (para [0007]) is modified to increase its serum half-life by pegylation (para [0173]-[0175]). It would have been obvious to one of ordinary skill in this art to use the PRO 140 antibody of Olson '408 for the CCR5 receptor antagonist of Olson '441. One of ordinary skill in this art would have been motivated to do so to increase the length of time between dose administrations for cost reduction.

Claim 94 lacks an inventive step under PCT Article 33(3) as being obvious over Nelson in view of Olson '441, as above, and further in view of Redfield.

Regarding claim 94, Redfield further teaches that the subject is a pregnant woman (para [0095]).

Claims 1-22, 24-28, 40-120, and 123-125 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.